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Pooled Analysis of RESOLUTE Clinical Trial Long-term Safety Data

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Background: Individual trials are often underpowered to show differences in rare adverse clinical events such as very late stent thrombosis (VLST; after one-year, definite + probable ST). The RESOLUTE clinical program comprises 5 trials prospectively designed with similar definitions, and adjudication procedures, that allows pooled analysis of clinical endpoints.
Methods: Over 5,000 patients treated with the Resolute zotarolimus-eluting stent (R-ZES) were pooled from the RESOLUTE All Comers randomized trial, comparing R-ZES (N = 1140; 2 yr follow-up) with the XIENCE V everolimus-eluting stent (EES, N=1152) and 4 single-arm studies: the RESOLUTE first-in-human (N = 139; R-FIM, 4 yr follow-up); the open label RESOLUTE International (N=2349; R-Int, 1 yr follow-up); RESOLUTE Japan (N=100; 1 yr follow-up); and RESOLUTE US (N=1402; 1 yr follow-up). Pooled safety endpoints (cardiac death, myocardial infarction [MI], and VLST) for R-ZES patients were compared with EES patients from Resolute All Comers. Pooled outcomes of single-vessel treated R-ZES patients (N = 2466) were compared with BMS-treated patients (N = 596) from the ENDEAVOR II randomized trial. RESOLUTE trials recommended six months dual antiplatelet therapy (DAPT); ENDEAVOR II patients received 12 weeks of DAPT. Propensity scores were used to adjust for differences in patient characteristics.
Results: At two years, the cumulative frequency of ST was 1.0% for R-ZES and EES (adjusted hazard ratio 1.335; p=0.424) and VLST was 0.2% for R-ZES and 0.3% for EES (adjusted hazard ratio 0.908; p=0.906). The cumulative ST rate for the single-lesion R-ZES subset was 0.3% and for the BMS group was 1.3% (adjusted hazard ratio 0.026, p=0.0125). The cumulative incidence of cardiac death or MI was similar for all the groups (R-ZES 5.4%, EES 6.2%, R-ZES subset 4.3%, BMS 5.8%; p=ns for both).
Conclusion: Pooled data analysis confirms a low rate of ST and VLST up to 2 years for R-ZES. Cardiac death or MI in patients treated with R-ZES through 2 years was similar to EES. Further analysis of data with longer follow-up (2 yr follow up of R-Int; 5 yr follow-up of R-FIM) will be presented.

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The Clopidogrel Resistance in Stent Thrombosis (CREST) Registry: The Case for Personalized Antiplatelet Therapy?

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Background: Current guidelines recommend standard doses of aspirin and clopidogrel following PCI. However, clinical studies show heterogeneity in responses to antiplatelet therapy (APT) and high residual platelet reactivity is associated with increased risk of adverse events, including stent thrombosis (ST). Individualized assessment of response to APT has not been widely implemented largely due to lack of a standardized and generally accepted platelet function test (PFT) appropriate for routine clinical use. We investigated the prevalence of APT hyporesponsiveness in ST and whether APT efficacy can be optimised with tailored therapy.
Methods: Between October 2009 and June 2011, 39 patients were admitted to our institution with definite ST. Response to aspirin and clopidogrel was measured following discharge using Short Thrombelastography (s-TEG), a simple, rapid and reproducible PFT that has been developed and validated by this group. Changes to APT were directed by s-TEG in hyporesponders and repeat testing undertaken following treatment modification.
Results: Median time from index PCI to ST was 1125 days. At presentation, 2 (5%) patients were on no APT (non-compliance), 11 (28%) were on both aspirin and clopidogrel, 1 (3%) was on clopidogrel alone and 25 (64%) were on aspirin alone. s-TEG testing showed that 12 (31%) patients had an adequate response to both aspirin and clopidogrel, 16 (41%) were hyporesponsive to clopidogrel alone, 1 (3%) was hyporesponsive to aspirin alone and 10 (26%) were hyporesponsive to both aspirin and clopidogrel. Treatment modification in hyporesponders included an increase in aspirin dose and/or changing clopidogrel to prasugrel. 3 patients who were hyporesponsive to both clopidogrel and prasugrel were switched to ticagrelor. Out of the 22 patients so far who have been retested following treatment modification, an adequate response to APT has been achieved in 19 (86%). None have presented with a further ST episode.
Conclusion: There is a high prevalence of hyporesponsiveness (69%) to aspirin and/or clopidogrel in patients with ST. Improved APT efficacy can be achieved by tailored therapy. s-TEG is a plausible PFT that can be used to deliver point-of-care personalized APT. Further data are required to investigate the possibility of dynamic changes in responses to APT and to determine whether tailored therapy leads to improved long term clinical outcomes.

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Stent Thrombosis after Implantation of XIENCE V Everolimus-Eluting Coronary Stent Systems in On-label and Off-label Populations: Pooled Two-Year Results from Seven XIENCE V Coronary Stent Trials

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Background: In light of the possible safety concerns from usage of drug-eluting stents in complex populations, determining whether differences exist between on-label (standard risk) or off-label (extended risk) use is important. Little is known in this regard with second generation stents.
Methods: Using all available data, we analyzed 13,259 patients (7,841 on- and 5,418 off-label) receiving XIENCE V everolimus-eluting coronary stent systems (Abbott Vascular, Santa Clara, CA) from 7 studies (3 pre-approval [SPIRIT II, III, IV] and 4 post-marketing [SPIRIT V and SPIRIT Women, XIENCE V USA, XIENCE V India]). Definite/probable ST was adjudicated per Academic Research Consortium definition by an independent clinical events committee.
Results: The 2-year cumulative ST rate in all patients receiving XIENCE V was 0.74%. Dual antiplatelet therapy compliance and ST rates up to 730 days are shown in the Table.

	XIENCE V Total Population n=13259	XIENCE V Standard Risk* (On-label) n=7841	XIENCE V Extended Risk† (Off-label) n=5418	p value‡ n=13259
	DAPT Compliance			
30 Days	90.3% (11959/13248)	92.1% 7216/7834)	87.6% (4743/5414)	<0.0001
180 Days	87.4% (11581/13248)	89.1% (6983/7834)	84.9% (4598/5414)	<0.0001
365 Days	78.5% (10394/13248)	78.9% (6179/7834)	77.9% (4215/5414)	0.1624
730 Days	59.5% (7880/13248)	59.5% (4664/7834)	59.4% (3216/5414)	0.8855
	ARC-Defined Stent Thrombosis (Definite/Probable)§			
Early ST (0-30 d)	0.34% (45/13178)	0.23% (18/7801)	0.50% (27/5377)	0.0098
Late ST (31-365 d)	0.28% (36/12867)	0.17% (13/7632)	0.44% (23/5235)	0.0060
Overall 1-Year ST (0-365 d)	0.62% (80/12885)	0.39% (30/7637)	0.95% (50/5248)	<0.0001
Very Late ST (365-730 d)	0.10% (13/12443)	0.12% (9/7411)	0.08% (4/5032)	0.5798
Overall 2-Year ST (0-730 d)	0.74% (93/12552)	0.52% (39/7456)	1.06% (54/5096)	<0.0001

*"Standard-risk" ("on-label") cohort characterized by eligibility criteria from the SPIRIT IV study.
†The "extended-risk" ("off-label") cohort characterized by the SPIRIT IV exclusion criteria, specifically defined as patients with any of the following: baseline lesion length >28 mm, reference vessel diameter <2·5 mm or >4·25 mm, chronic total occlusion, graft lesion, bifurcation with side branch ≥2 mm, ostial, left main, in-stent restenosis, more than two lesions stented in the same vessel, more than two vessels treated, acute myocardial infarction, renal insufficiency, or ejection fraction <30%.
‡From Fisher's Exact Test comparing Standard Risk vs. Extended Risk
§ARC = Academic Research Consortium

Conclusion: In this large, patient-level pooled safety analysis, the 2-year cumulative ST rate in all patients receiving XIENCE V was 0.74% and was higher in the first year with off-label use (0.39% on-label vs. 0.95% off-label). ST was uncommon after year 1 with everolimus-eluting stents (~0.1%) irrespective of on- or off-label usage.

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Stent Thrombosis and Dual Antiplatelet Interruption: Insights from the XIENCE V Everolimus-Eluting Coronary Stent System Trials

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Background: Dual antiplatelet therapy (DAPT) interruption prior to 180 days (d) with first generation DES is associated with a higher risk of stent thrombosis (ST). We